PCT/EP 03 / 12035

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Request for grant of a patent

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The Patent Office

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1.	Your Reference	JAF/PG4979
2.	Patent application number *(The Patent office will fill in this part)*	0225028.0
		28 OCT 2002
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	GLAXO GROUP LIMITED GLAXO WELLCOME HOUSE BERKELEY AVENUE GREENFORD MIDDLESEX UB6 ONN GB
	Patents ADP number *(if you know it)*	07358703
	If the applicant is a corporate body, give the country/state of its corporation	GB
4	Title of the invention	CHEMICAL COMPOUNDS
5	Name of your agent *(if you know one)*	JUDITH PRITCHARD
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	GLAXOSMITHKLINE CORPORATE INTELLECTUAL PROPERTY 980 GREAT WEST ROAD BRENTFORD, MIDDLESEX TW8 9GS, GB
	Patents ADP number *(if you know it)*	80725550004

6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.*	YES

See note (d))

Patents Form 1/77

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Description	30
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Abstract	1
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10. If you are also filing any of the following, state how many against each item

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Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. Judith Pritchard.

I/We request the grant of a patent on the basis of this application

Signature JUDITH PRITCHARD 25 October 2002
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

LESLEY WELLS

01438 76 8599

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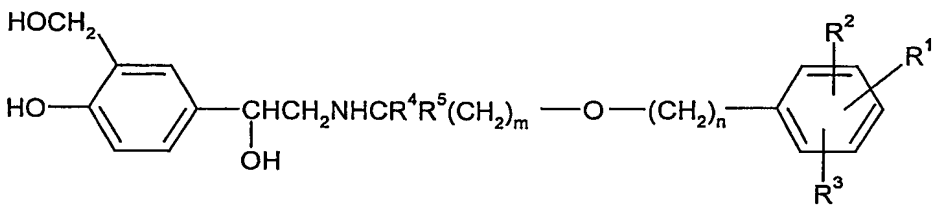
Chemical Compounds

The present invention is concerned with phenethanolamine derivatives, processes for their preparation, compositions containing them and their use in medicine, particularly in the prophylaxis and treatment of respiratory diseases.

Certain phenethanolamine compounds are known in the art as having selective stimulant action at β_2-adrenoreceptors and therefore having utility in the treatment of bronchial asthma and related disorders. Thus GB 2 140 800 describes phenethanolamine compounds including 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol 1-hydroxy-2-naphthalenecarboxylate (salmeterol xinafoate) which is now used clinically in the treatment of such medical conditions.

Although salmeterol and the other commercially available β_2-adrenoreceptor agonists are effective bronchodilators, the maximum duration of action is 12 hours, hence twice daily dosing is often required. There is therefore a clinical need for compounds having potent and selective stimulant action at β_2-adrenoreceptors and having an advantageous profile of action.

According to the present invention, there is provided a compound of formula (I)



(I)

or a salt, solvate, or physiologically functional derivative thereof, wherein:

m is an integer of from 2 to 8;
n is an integer of from 3 to 11, preferably from 3 to 7;
with the proviso that m + n is 5 to 19, preferably 5 to 12;

R^1 is SR^6, SOR^6, or SO_2R^6,
wherein R^6 is a C_{3-7}cycloalkyl or C_{3-7}cycloalkenyl group;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, halo, phenyl, and C_{1-6}haloalkyl; and

R^4 and R^5 are independently selected from hydrogen and C_{1-4}alkyl with the proviso that the total number of carbon atoms in R^4 and R^5 is not more than 4.

In the compounds of formula (I) the group R^1 is preferably attached to the meta-position relative to the $-O-(CH_2)_n-$ link.

R^1 preferably represents SOR^6.

R^6 preferably represents cyclopentyl.

R^4 and R^5 are preferably independently selected from hydrogen and methyl, more preferably R^4 and R^5 are both hydrogen.

m is suitably 4, 5, or 6, and n is suitably 2, 3, 4, 5 or 6. Preferably m is 5 or 6 and n is 3 or 4, such that m + n is 8, 9 or 10, preferably 9.

It will be appreciated that the compounds of formula (I) include two asymmetric centres, namely the carbon atom of the

group and, when R^1 represents SOR^6, at the sulphur atom of the sulphoxide group The compounds may therefore exist in four different isomeric forms. The present invention includes both (S) and (R) enantiomers at both chiral centres either in substantially pure form or admixed in any proportions.

Similarly, where R^4 and R^5 are different groups, the carbon atom to which they are attached is an asymmetric centre and the present invention includes both (S) and (R) enantiomers at this centre either in substantially pure form or admixed in any proportions.

Thus the compounds of formula (I) include all enantiomers and diastereoisomers as well as mixtures thereof in any proportions.

Salts and solvates of compounds of formula (I) which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formula (I) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives.

By the term "physiologically functional derivative" is meant a chemical derivative of a compound of formula (I) having the same physiological function as the parent compound of formula (I) for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters.

Suitable salts according to the invention include those formed with both organic and inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, triphenylacetic, sulphamic, sulphanilic, succinic, oxalic, fumaric, maleic, malic, glutamic, aspartic, oxaloacetic, methanesulphonic, ethanesulphonic, arylsulphonic (for example p-toluenesulphonic, benzenesulphonic, naphthalenesulphonic or naphthalenedisulphonic), salicylic, glutaric, gluconic, tricarballylic, cinnamic, substituted cinnamic (for example, phenyl, methyl , methoxy or halo substituted cinnamic, including 4-methyl and 4-methoxycinnamic acid), ascorbic, oleic, naphthoic, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), naphthaleneacrylic (for example naphthalene-2-acrylic), benzoic, 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic, 4-phenylbenzoic, benzeneacrylic (for example 1,4-benzenediacrylic) and isethionic acids. Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases such as dicyclohexyl amine and N-methyl-D-glucamine.

Pharmaceutically acceptable esters of the compounds of formula (I) may have a hydroxyl group converted to a C_{1-6}alkyl, aryl, aryl C_{1-6} alkyl, or amino acid ester.

As mentioned above, the compounds of formula (I) are selective β_2-adrenoreceptor agonists as demonstrated using functional or reporter gene readout from cell lines transfected with human beta-adrenoreceptors as described below. Compounds according to the present invention also have the potential to combine long duration of effect with rapid onset of action. Furthermore, certain compounds have shown an improved therapeutic index in animal models relative to existing long-acting β_2-agonist bronchodilators. As such, compounds of the invention may be suitable for once-daily administration.

Compounds of formula (I) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have use in the prophylaxis and treatment of clinical conditions for which a selective β_2-adrenoreceptor agonist is indicated. Such conditions include diseases associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease (e.g. rhinitis, including seasonal and allergic rhinitis).

Other conditions which may be treated include premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

Accordingly, the present invention provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2-adrenoreceptor agonist is indicated, which comprises administration of a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. In particular, the present invention provides such a method for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect the present invention provides such a method for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive

heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) or muscle wasting disease.

In the alternative, there is also provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy, particularly, for use in the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2-adrenoreceptor agonist is indicated. In particular, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) or muscle wasting disease.

The present invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a selective β_2-adrenoreceptor agonist is indicated, for example a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

The amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. The compounds of the invention may be administered by inhalation at a dose of from 0.0005mg to 10 mg, preferably 0.005mg to 0.5mg. The dose range for adult humans is generally from 0.0005 mg to 100mg per day and preferably 0.01 mg to 1mg per day.

While it is possible for the compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to be administered alone, it is preferable to present it as a pharmaceutical formulation.

Accordingly, the present invention further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

Hereinafter, the term "active ingredient" means a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example saline or water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Formulations generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base (carrier substance) such as lactose or starch. Use of lactose is preferred. Each capsule or cartridge may generally contain between 20μg-10mg of the compound of formula (I) optionally in combination with another therapeutically active ingredient. Alternatively, the compound of the invention may be presented without

excipients. Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi-dose delivery, the formulation can be pre-metered (eg as in Diskus, see GB 2242134 or Diskhaler, see GB 2178965, 2129691 and 2169265) or metered in use (eg as in Turbuhaler, see EP 69715). An example of a unit-dose device is Rotahaler (see GB 2064336). The Diskus inhalation device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing a compound of formula (I) preferably combined with lactose. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the said leading end portions is constructed to be attached to a winding means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the said base sheet.

Spray compositions for topical delivery to the lung by inhalation may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the compound of formula (I) optionally in combination with another therapeutically active ingredient and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof. Carbon dioxide or other suitable gas may also be used as propellant. The aerosol composition may be excipient free or may optionally contain additional formulation excipients well known in the art such as surfactants eg oleic acid or lecithin and cosolvents eg ethanol. Pressurised formulations will generally be retained in a canister (eg an aluminium canister) closed with a valve (eg a metering valve) and fitted into an actuator provided with a mouthpiece.

Medicaments for administration by inhalation desirably have a controlled particle size. The optimum particle size for inhalation into the bronchial system is usually 1-10μm, preferably 2-5μm. Particles having a size above 20μm are generally too large when

inhaled to reach the small airways. To achieve these particle sizes the particles of the active ingredient as produced may be size reduced by conventional means eg by micronisation. The desired fraction may be separated out by air classification or sieving. Preferably, the particles will be crystalline. When an excipient such as lactose is employed, generally, the particle size of the excipient will be much greater than the inhaled medicament within the present invention. When the excipient is lactose it will typically be present as milled lactose, wherein not more than 85% of lactose particles will have a MMD of 60-90μm and not less than 15% will have a MMD of less than 15μm.

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

Solutions for inhalation by nebulation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose an acacia.

Preferred unit dosage formulations are those containing an effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The compounds and pharmaceutical formulations according to the invention may be used in combination with or include one or more other therapeutic agents, for example selected from anti-inflammatory agents, anticholinergic agents (particularly an M_1, M_2, M_1/M_2 or M_3 receptor antagonist), other β_2-adrenoreceptor agonists, antiinfective agents (e.g. antibiotics, antivirals), or antihistamines. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with one or more other therapeutically active agents, for example selected from an anti-inflammatory agent (for example a corticosteroid or an NSAID), an anticholinergic agent, another β_2-adrenoreceptor agonist, an antiinfective agent (e.g. an antibiotic or an antiviral), or an antihistamine. Preferred are combinations comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a corticosteroid, and/or an anticholinergic, and/or a PDE-4 inhibitor. Preferred combinations are those comprising one or two other therapeutic agents.

It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, (e.g. as alkali metal or amine salts or as acid addition salts), or prodrugs, or as esters (e.g. lower alkyl esters), or as solvates (e.g. hydrates) to optimise the activity and/or stability and/or physical characteristics (e.g. solubility) of the therapeutic ingredient. It will be clear also that where appropriate, the therapeutic ingredients may be used in optically pure form.

Suitable anti-inflammatory agents include corticosteroids and NSAIDs. Suitable corticosteroids which may be used in combination with the compounds of the invention are those oral and inhaled corticosteroids and their pro-drugs which have anti-inflammatory activity. Examples include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester, 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy- androsta-1,4-diene-17β-carbothioic acid *S*-(2-oxo-tetrahydro-furan-3S-yl) ester, beclomethasone esters (e.g. the 17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolide, mometasone esters (e.g. the furoate ester), triamcinolone acetonide, rofleponide, ciclesonide, butixocort propionate, RPR-106541, and ST-126. Preferred corticosteroids include fluticasone propionate, 6α,9α-difluoro-11β-hydroxy-16α-methyl-

17α-[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester and 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester, more preferably 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester.

Suitable NSAIDs include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (e.g. theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine antagonists (e.g. chemokine antagonists) or inhibitors of cytokine synthesis. Suitable other β_2-adrenoreceptor agonists include salmeterol (e.g. as the xinafoate), salbutamol (e.g. as the sulphate or the free base), formoterol (e.g. as the fumarate), fenoterol or terbutaline and salts thereof.

Of particular interest is use of the compound of formula (I) in combination with a phosphodiesterase 4 (PDE4) inhibitor or a mixed PDE3/PDE4 inhibitor. The PDE4-specific inhibitor useful in this aspect of the invention may be any compound that is known to inhibit the PDE4 enzyme or which is discovered to act as a PDE4 inhibitor, and which are only PDE4 inhibitors, not compounds which inhibit other members of the PDE family as well as PDE4. Generally it is preferred to use a PDE4 inhibitor which has an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC_{50} for the form which binds rolipram with a low affinity. For the purposes of this disclosure, the cAMP catalytic site which binds R and S rolipram with a low affinity is denominated the "low affinity" binding site (LPDE 4) and the other form of this catalytic site which binds rolipram with a high affinity is denominated the "high affinity" binding site (HPDE 4). This term "HPDE4" should not be confused with the term "hPDE4" which is used to denote human PDE4.

A method for determining IC_{50}s ratios is set out in US patent 5,998,428 which is incorporated herein in full by reference as though set out herein. See also PCT application WO 00/51599 for an another description of said assay. Compounds

A further refinement of this standard is that of one wherein the PDE4 inhibitor has an IC_{50} ratio of about 0.1 or greater; said ratio is the ratio of the IC_{50} value for competing with the binding of 1nM of [^{3}H]R-rolipram to a form of PDE4 which binds rolipram with a high affinity over the IC_{50} value for inhibiting the PDE4 catalytic activity of a form which binds rolipram with a low affinity using 1 μM[^{3}H]-cAMP as the substrate.

Examples of useful PDE4 inhibitors are:
(R)-(+)-1-(4-bromobenzyl)-4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidone;
(R)-(+)-1-(4-bromobenzyl)-4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidone;
3-(cyclopentyloxy-4-methoxyphenyl)-1-(4-N'-[N2-cyano-S-methyl-isothioureido]benzyl)-2-pyrrolidone;
cis 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid];
cis-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol];
(R)-(+)-ethyl [4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidine-2-ylidene]acetate; and
(S)-(-)-ethyl [4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidine-2-ylidene]acetate.

Most preferred are those PDE4 inhibitors which have an IC_{50} ratio of greater than 0.5, and particularly those compounds having a ratio of greater than 1.0. Preferred compounds are *cis* 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one and *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]; these are examples of compounds which bind preferentially to the low affinity binding site and which have an IC_{50} ratio of 0.1 or greater.

Other compounds of interest include:
Compounds set out in U.S. patent 5,552,438 issued 03 September, 1996; this patent and the compounds it discloses are incorporated herein in full by reference. The compound of particular interest, which is disclosed in U.S. patent 5,552,438, is *cis*-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid (also known as cilomalast) and its salts, esters, pro-drugs or physical forms;

AWD-12-281 from Asta Medica (Hofgen, N. et al. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.98; CAS reference No. 247584020-9); a 9-benzyladenine derivative nominated NCS-613 (INSERM); D-4418 from Chiroscience

and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-168787) and attributed to Pfizer; a benzodioxole derivative disclosed by Kyowa Hakko in WO99/16766; K-34 from Kyowa Hakko; V-11294A from Napp (Landells, L.J. et al. Eur Resp J [Annu Cong Eur Resp Soc (Sept 19-23, Geneva) 1998] 1998, 12 (Suppl. 28): Abst P2393); roflumilast (CAS reference No 162401-32-3) and a pthalazinone (WO99/47505, the disclosure of which is hereby incorporated by reference) from Byk-Gulden; Pumafentrine, (-)-p-[(4*a*R*,10*b*S*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[c][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide which is a mixed PDE3/PDE4 inhibitor which has been prepared and published on by Byk-Gulden, now Altana; arofylline under development by Almirall-Prodesfarma; VM554/UM565 from Vemalis; or T-440 (Tanabe Seiyaku; Fuji, K. et al. J Pharmacol Exp Ther,1998, 284(1): 162), and T2585.

Other possible PDE-4 and mixed PDE3/PDE4 inhibitors include those listed in WO01/13953, the disclosure of which is hereby incorporated by reference.

Suitable anticholinergic agents are those compounds that act as antagonists at the muscarinic receptor, in particular those compounds which are antagonists of the M_1 and M_2 receptors. Exemplary compounds include the alkaloids of the belladonna plants as illustrated by the likes of atropine, scopolamine, homatropine, hyoscyamine; these compounds are normally administered as a salt, being tertiary amines. These drugs, particularly the salt forms, are readily available from a number of commercial sources or can be made or prepared from literature data via, to wit:

Atropine - CAS-51-55-8 or CAS-51-48-1 (anhydrous form), atropine sulfate - CAS-5908-99-6; atropine oxide - CAS-4438-22-6 or its HCl salt - CAS-4574-60-1 and methylatropine nitrate - CAS-52-88-0.

Homatropine - CAS-87-00-3, hydrobromide salt - CAS-51-56-9, methylbromide salt - CAS-80-49-9.

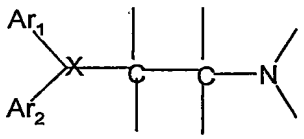
Hyoscyamine (*d*, *l*) - CAS-101-31-5, hydrobromide salt - CAS-306-03-6 and sulfate salt - CAS-6835-16-1.

Scopolamine - CAS-51-34-3, hydrobromide salt - CAS-6533-68-2, methylbromide salt-CAS-155-41-9.

Preferred anticholinergics include ipratropium (e.g. as the bromide), sold under the name Atrovent, oxitropium (e.g. as the bromide) and tiotropium (e.g. as the bromide) (CAS-139404-48-1). Also of interest are: methantheline (CAS-53-46-3), propantheline

bromide (CAS- 50-34-9), anisotropine methyl bromide or Valpin 50 (CAS- 80-50-2), clidinium bromide (Quarzan, CAS-3485-62-9), copyrrolate (Robinul), isopropamide iodide (CAS-71-81-8), mepenzolate bromide (U.S. patent 2,918,408), tridihexethyl chloride (Pathilone, CAS-4310-35-4), and hexocyclium methylsulfate (Tral, CAS-115-63-9). See also cyclopentolate hydrochloride (CAS-5870-29-1), tropicamide (CAS-1508-75-4), trihexyphenidyl hydrochloride (CAS-144-11-6), pirenzepine (CAS-29868-97-1), telenzepine (CAS-80880-90-9), AF-DX 116, or methoctramine, and the compounds disclosed in WO01/04118, the disclosure of which is hereby incorporated by reference.

Suitable antihistamines (also referred to as H_1-receptor antagonists) include any one or more of the numerous antagonists known which inhibit H_1-receptors, and are safe for human use. All are reversible, competitive inhibitors of the interaction of histamine with H_1-receptors. The majority of these inhibitors, mostly first generation antagonists, have a core structure, which can be represented by the following formula:



This generalized structure represents three types of antihistamines generally available: ethanolamines, ethylenediamines, and alkylamines. In addition, other first generation antihistamines include those which can be characterized as based on piperizine and phenothiazines. Second generation antagonists, which are non-sedating, have a similar structure-activity relationship in that they retain the core ethylene group (the alkylamines) or mimic the tertiary amine group with piperizine or piperidine. Exemplary antagonists are as follows:

Ethanolamines: carbinoxamine maleate, clemastine fumarate, diphenylhydramine hydrochloride, and dimenhydrinate.

Ethylenediamines: pyrilamine amleate, tripelennamine HCl, and tripelennamine citrate.

Alkylamines: chlropheniramine and its salts such as the maleate salt, and acrivastine.

Piperazines: hydroxyzine HCl, hydroxyzine pamoate, cyclizine HCl, cyclizine lactate, meclizine HCl, and cetirizine HCl.

Piperidines: Astemizole, levocabastine HCl, loratadine or its descarboethoxy analogue, and terfenadine and fexofenadine hydrochloride or another pharmaceutically acceptable salt.

Azelastine hydrochloride is yet another H_1 receptor antagonist which may be used in combination with a PDE4 inhibitor.

Examples of preferred anti-histamines include methapyrilene and loratadine.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a corticosteroid.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an antihistamine.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor and a corticosteroid.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic and a PDE-4 inhibitor.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a physiologically acceptable diluent or carrier represent a further aspect of the invention.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

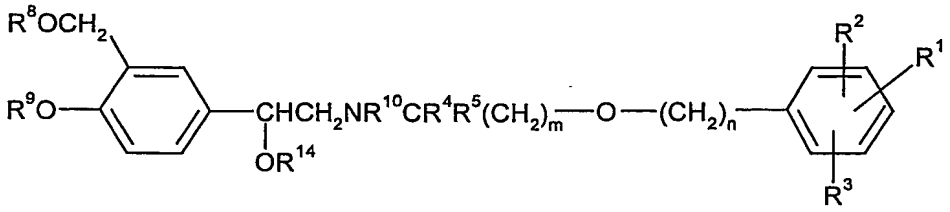
According to a further aspect of the invention, there is provided a process for preparing a compound of formula (I) or a salt, solvate, or physiologically functional derivative thereof which comprises a process as defined below followed by the following steps in any order:

(i) optional removal of any protecting groups;

(ii) optional separation of an enantiomer from a mixture of enantiomers;

(iii) optional conversion of the product to a corresponding salt, solvate, or physiologically functional derivative thereof.

In one general process (a), a compound of formula (I), may be obtained by deprotection of a protected intermediate, for example of formula (II):



(II)

or a salt or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, m, and n are as defined for the compound of formula (I), R^8, R^9, and R^{10} are each independently either hydrogen or a protecting group provided that at least one of R^8, R^9, and R^{10} is a protecting group, and R^{14} is either hydrogen or a protecting group.

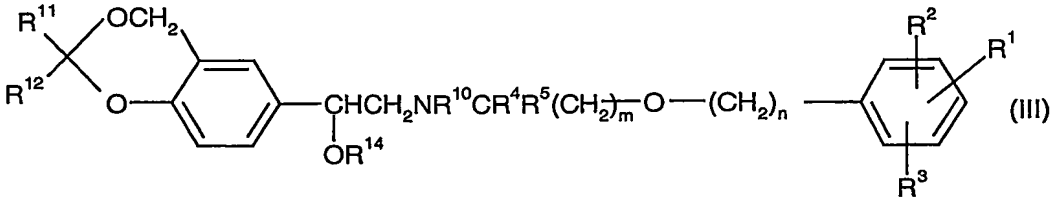
Suitable protecting groups may be any conventional protecting group such as those described in "Protective Groups in Organic Synthesis" by Theodora W Greene and Peter G M Wuts, 3rd edition (John Wiley & Sons, 1999). Examples of suitable hydroxyl protecting groups represented by R^8 and R^9 are esters such as acetate ester, aralkyl groups such as benzyl, diphenylmethyl, or triphenylmethyl, and tetrahydropyranyl.

Examples of suitable amino protecting groups represented by R^{10} include benzyl, α-methylbenzyl, diphenylmethyl, triphenylmethyl, benzyloxycarbonyl, tert-butoxycarbonyl, and acyl groups such as trichloroacetyl or trifluoroacetyl.

As will be appreciated by the person skilled in the art, use of such protecting groups may include orthogonal protection of groups in the compounds of formula (II) to facilitate the selective removal of one group in the presence of another, thus enabling selective functionalisation of a single amino or hydroxyl function. For example, the –CH(OH) group may be orthogonally protected as $-CHOR^{14}$ using, for example, a trialkylsilyl group such as triethylsilyl. A person skilled in the art will also appreciate other orthogonal protection strategies, available by conventional means as described in Theodora W Greene (see above).

The deprotection to yield a compound of formula (I) may be effected using conventional techniques. Thus, for example, when R^8, R^9, and/or R^{10} is an aralkyl group, this may be cleaved by hydrogenolysis in the presence of a metal catalyst (e.g. palladium on charcoal).

When R^8 and/or R^9 is tetrahydropyranyl this may be cleaved by hydrolysis under acidic conditions. Acyl groups represented by R^{10} may be removed by hydrolysis, for example with a base such as sodium hydroxide, or a group such as trichloroethoxycarbonyl may be removed by reduction with, for example, zinc and acetic acid. Other deprotection methods may be found in Theodora W Greene (see above). In a particular embodiment of process (a), R^8 and R^9 may together represent a protecting group as in the compound of formula (III).



(III)

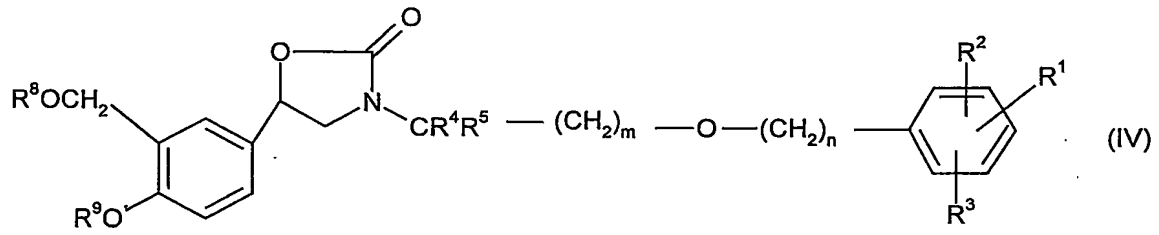
or a salt or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, R^{10}, R^{14}, m, and n are as defined for the compound of formula (I) R^{11} and R^{12} are independently selected from hydrogen,

C_{1-6}alkyl, or aryl or R^{11} and R^{12} together form a C_{3-7} alkyl group. In a preferred aspect, both R^{11} and R^{12} are methyl.

A compound of formula (III) may be converted to a compound of formula (I) by hydrolysis with dilute aqueous acid, for example acetic acid or hydrochloric acid in a suitable solvent or by transketalisation in an alcohol, for example ethanol, in the presence of a catalyst such as an acid (for example, toluenesulphonic acid) or a salt (such as pyridinium tosylate) at normal or elevated temperature.

It will be appreciated that the protecting groups R^8, R^9, R^{10} and R^{14} (including the cyclised protecting group formed by R^8 and R^9 as depicted in formula (III) may be removed in a single step or sequentially. The precise order in which protecting groups are removed will in part depend upon the nature of said groups and will be readily apparent to the skilled worker. Preferably, when R^8 and R^9 together form a protecting group as in formula (III) this protecting group is removed together with any protecting group on the CH(OH) moiety, followed by removal of R^{10}.

Compounds of formulae (II) and (III) wherein R^{10} is hydrogen may be prepared from the corresponding compound of formula (IV):

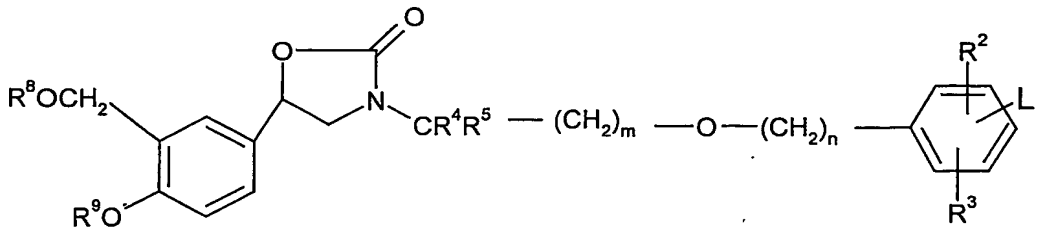


(IV)

or a salt or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, R^8, R^9 m, and n are as defined for the compound of formula (II) or (III).

The conversion of a compound of formula (IV) to a compound of formula (II) or (III) may be effected by treatment with a base, for example a non-aqueous base, such as potassium trimethylsilanolate, or an aqueous base such as aqueous sodium hydroxide, in a suitable solvent such as tetrahydrofuran.

Compounds of formula (IV) wherein R^1 represents a group SR^6 may be prepared from the corresponding compound of formula (V):



(V)

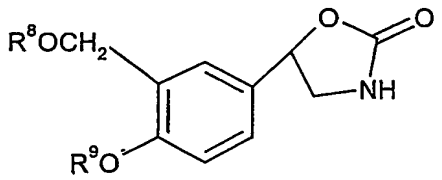
wherein R^2, R^3, R^4, R^5, R^8, R^9, m, and n are as defined for formula (II) and L is a leaving group, for example a halo group, (preferably iodo);

by reaction with a compound R^6SH in the presence of 1,1 bis-(diphenylphosphine)ferrocene, tris(dibenzylidene acetone) di-palladium, N-methylpyrrolidinone and an organic base such as triethylamine. The sulfide product initially obtained from this reaction may if desired be oxidised to give the corresponding compound of formula (IV) wherein R^1 represents a group SOR^6. Oxidation may be carried out using conventional oxidising agents, for example sodium periodate, in a suitable solvent, for example an alcohol such as ethanol.

When R^1 represents SOR^6 the product may initially be obtained as a mixture of diastereoisomers. These may be separated by conventional methods, for example using chiral chromatography, such as chiral HPLC. Alternatively the sulphoxides can be prepared selectively in one of the diastereomeric forms by the use of a chiral oxidising agent.

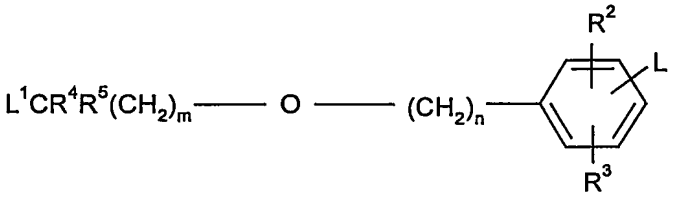
A compound of formula (IV) wherein R^1 represents SO_2R^6 may be prepared by oxidation of a corresponding compound of formula (IV) wherein R^1 represents SOR^6 or SR^6 by reaction with a peracid, for example metachlorperbenzoic acid. When a sulfide (ie R^1 represents SR^6) is employed as the starting material, the peracid should be used in excess, to ensure complete oxidation.

Compounds of formula (V) may be prepared by coupling a compound of formula (VI):



(VI)

or a salt or solvate thereof, wherein R^8 and R^9 are as defined for the compound of formula (V) with a compound of formula (VII):



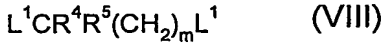
(VII)

wherein R^4, R^5, L m and n are as defined for the compound of formula (V) and L^1 is a leaving group, for example a halo group (typically bromo or iodo) or a sulphonate such as an alkyl sulphonate (typically, methanesulphonate), an arylsulphonate (typically, toluenesulphonate), or a haloalkyl sulphonate (typically, trifluoromethanesulphonate).

The coupling of a compound of formula (VI) with a compound of formula (VII) may be effected in the presence of a base, such as a metal hydride, for example sodium hydride, or an inorganic base such as cesium carbonate, in an aprotic solvent, for example N,N-dimethylformamide or tetrahydrofuran.

Compounds of formula (VI) may be prepared for example as described in WO 02/066422.

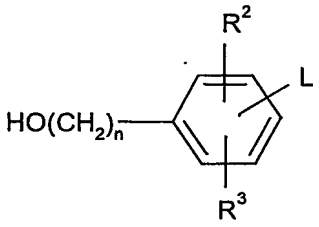
Compounds of formula (VII) may be prepared from the corresponding dihaloalkane of formula (VIII):



(VIII)

wherein R^4, R^5 and m are as defined for compounds of formula (I) and each L^1 represents a halo, typically bromo;

by reaction with an alcohol of formula (IX):



(IX)

wherein R^2, R^3, L and n are as defined for compounds of formula (VII).

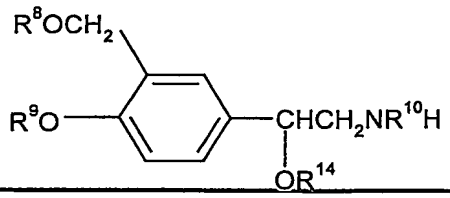
The coupling of compounds (VIII) and (IX) may be effected in the presence of an inorganic base, such as aqueous sodium hydroxide, under phase transfer conditions in the presence of a salt such as tetraalkylammonium bromide.

Compounds of formula (VIII) and (IX) are known or may be prepared by standard methods.

It will be appreciated that when the group L in compounds of formula (VII) represents bromo, this may, if desired, be exchanged for an iodo substituent by reaction with iodine in the presence of an alkyl lithium, such as n-butyl lithium, in a solvent such as tetrahydrofuran.

Compounds of formula (II) or (III) wherein R^{10} is a protecting group may be prepared as described in process (b) below.

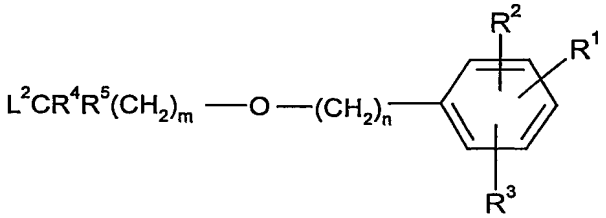
In a further process (b), a compound of formula (I) may be obtained by alkylation of an amine of formula (X):



(X)

wherein R^8, R^9, R^{10} and R^{14} are each independently either hydrogen or a protecting group. Suitable protecting groups are discussed in the definition of compounds of formula (II);

with a compound of formula (XI):



(XI)

wherein R^1, R^2, R^3, R^4, R^5, m, and n are as defined for the compound of formula (I) and L^2 is a leaving group such as halo (typically bromo); followed by removal of any protecting groups present by conventional methods as described above for the deprotection of compounds of formula (II).

The reaction of compounds of formulae (X) and (XI) is optionally effected in the presence of an organic base such as a trialkylamine, for example, diisopropylethylamine, and in a suitable solvent for example dimethyl formamide.

Compounds of formula (X) are known in the art (for example EP-A 0947498 or WO 02/070490) or may be readily prepared by a person skilled in the art.

Compounds of formula (XI) may be prepared from a compound of formula (VII) by reaction with a compound R^6SH in an analagous manner to the conversion of a compound of formula (V) into a compound of formula (IV).

It will be appreciated that in any of the routes described above, the precise order of the synthetic steps by which the various groups and moieties are introduced into the

molecule may be varied. It will be within the skill of the practitioner in the art to ensure that groups or moieties introduced at one stage of the process will not be affected by subsequent transformations and reactions, and to select the order of synthetic steps accordingly.

The enantiomeric compounds of the invention may be obtained (i) by separation of the components of the corresponding racemic mixture, for example, by means of a chiral chromatography column, enzymic resolution methods, or preparing and separating suitable diastereoisomers, (ii) by direct synthesis from the appropriate chiral intermediates by the methods described above, or (iii) by enantioselective oxidation of the sulphur atom.

Optional conversions of a compound of formula (I) to a corresponding salt may conveniently be effected by reaction with the appropriate acid or base. Optional conversion of a compound of formula (I) to a corresponding solvate or physiologically functional derivative may be effected by methods known to those skilled in the art.

For a better understanding of the invention, the following Examples are given by way of illustration.

SYNTHETIC EXAMPLES

Throughout the examples, the following abbreviations are used:

LC: Liquid Chromatography

LCMS: Liquid Chromatography Mass Spectrometry.

RT : retention time

THF : tetrahydofuran

DMF : N,N-dimethylformamide

bp : boiling point

ca : circa

h : hour(s)

min : minute(s)

All temperatures are given in degrees centigrade.
Silica gel refers to Merck silica gel 60 Art number 7734.
Flash silica gel refers to Merck silica gel 60 Art number 9385.
Biotage refers to prepacked silica gel cartridges containing KP-Sil run on flash 12i chromatography module.
Bond Elut are prepacked cartridges used in parallel purifications, normally under vacuum. These are commercially available from Varian.

NMR experiments at 400MHz (unless specified otherwise).

LCMS was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm x 4.6 mm ID) eluting with 0.1% HCO_2H and 0.01 M ammonium acetate in water (solvent A), and 0.05% HCO_2H 5% water in acetonitrile (solvent B), using the following elution gradient 0-0.7 min 0%B, 0.7-4.2 min 100%B, 4.2-5.3 min 0%B, 5.3-5.5 min 0%B at a flow rate of 3 ml/min. The mass spectra were recorded on a Fisons VG Platform spectrometer using electrospray positive and negative mode (ES+ve and ES-ve).

Example 1

4-{(1*R*)-2-[(6-{4-[3-(Cyclopentylsulfinyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol acetate

i) 6-Bromohexyl 4-(3-bromophenyl)butyl ether

A stirred mixture of 4–(3-bromophenyl) butan-1-ol (18 g) (EP 0 995 752A1), 1,6 dibromohexane (48 ml), tetrabutylammonium bromide (1.5 g) and 50% aqueous sodium hydroxide solution (500 ml) was stirred for 2 days at ambient temperature. The mixture was poured into water (1000 ml) and extracted into ethyl acetate. The combined extracts were washed with water, dried (Na_2SO_4) and evaporated. The residual oil was purified on the biotage eluting with light petroleum (40-60 °C), and then light petroleum (40-60 °C) - ether (9:1). The appropriate fractions were evaporated to give the *title compound* (18 g) LCMS RT=4.34 min.

ii) 6-Bromohexyl 4-(3-iodophenyl)butyl ether

A solution of n-butyl lithium in hexane (1.6 M; 50 ml) was added to a stirred solution of 6-bromophenyl 4-(3-bromophenyl)butyl ether (21 g) in dry THF (150 ml) at –85 °C under nitrogen. After 15 min a solution of iodine (19.8 g) in THF (100 ml) was added dropwise over 20 min. The solution was then allowed to warm up to 0 °C and aqueous sodium bisulphite was added. The mixture was poured into water and extracted into ether. The combined extracts were dried (Na_2SO_4) and evaporated. The residue was purified by flash silica gel column chromatography (1 kg) eluting with cyclohexane – ether (9:1). The appropriate fractions were evaporated to give *the title compound* (17 g). LCMS RT=4.41 min.

iii) Di(tert-butyl) 2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxoethylimidodicarbonate

Cesium carbonate (70.4g) was added to a stirred suspension of 2-bromo-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanone, (Glaxo, DE 3513885, 1985) (61.8g) and di-t-butyl iminodicarboxylate (47.15g) in acetonitrile (600ml) under nitrogen. After vigorous stirring at 21° for 24 h the mixture was diluted with water (*ca*800ml) and the product was extracted with diethyl ether (1litre, then 200ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated to *ca*400ml. The white crystals were collected by filtration, washed with diethyl ether and dried to give the *title compound* (24.4g) δ ($CDCl_3$) 7.78(1H, dd, J 8, 2Hz), 7.65 (1H, brs), 6.87(1H, d, J 8Hz), 4.97(2H, s), 4.88(2H, s), 1.56(6H, s) and 1.48 (18H, s) . Further concentration of the mother liquors gave additional product (13.8g). A third crop (7.1g) was obtained by chromatographing the mother liquors on silica gel, evaporating the appropriate eluate and triturating with diethyl ether.

iv) tert-Butyl 2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxoethylcarbamate

Trifluoroacetic acid (92ml) was added to a stirred solution of di(tert-butyl) 2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxoethylimidodicarbonate, (352.55g) in dichloromethane (3.6litres) at 21° and the reaction was stirred for 1.5 h. Aqueous NaOH solution (1.75litres) was added and after 10 min the phases were separated. The organic layer was washed with water, dried ($MgSO_4$) and evaporated to an oil. This was stored under high vacuum overnight and then triturated with hexane:ether (3:1) to give the crude product (226.61g). This was purified by recrystallisation from diethyl ether to give the *title compound* (122.78g). Further product (61.5g) was obtained from the mother liquors by evaporation and chromatography on a Biotage using 15% ethyl acetate in hexane. LCMS RT = 3.37min.

v) tert-Butyl (2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethylcarbamate

A 2M solution of borane - dimethyl sulphide in THF (28ml) was added slowly to a 1M solution of (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole in toluene (56ml) at 0° under nitrogen. A solution of tert-butyl 2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxoethylcarbamate, (108.2g) in THF (1.3litres) was added slowly keeping the temperature below 5° followed by 2M solution of borane - dimethyl sulphide in THF (252ml) over 50 min. After 1 h, 2M HCl (170ml) was added with cooling and the mixture was partitioned between ethyl acetate and water . The organic layer was washed with saturated $NaHCO_3$ solution and brine and dried ($MgSO_4$). The solution was concentrated and the product purified by chromatography on flash silica gel (800g), eluting successively with hexane:ethyl acetate (4:1 then 3:1) to give the *title compound* (93.3g), LCMS RT = 3.31min.

vi) (5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

tert-Butyl (2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethylcarbamate, (86.37g) in DMF (600ml) was added dropwise to a stirred suspension of sodium hydride (60% oil dispersion, 11.9g) in DMF (160ml) with cooling such that the internal temperature remained at 0° under nitrogen. The mixture was stirred at 21° for 2 h. The mixture was recooled to 0° and 2M HCl (134ml) was added. The mixture was diluted with water and the product was extracted with ethyl acetate twice. The solution was washed with brine twice, dried ($MgSO_4$) and evaporated to give the *title compound* (63.55g) LCMS RT = 2.66min.

vii) (5R)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-{6-[4-(3-iodophenyl)butoxy]hexyl}-1,3-oxazolidin-2-one

Sodium hydride (60% dispersion in oil 1.26 g) was added to a stirred, cooled (ice-bath) solution of (5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxazolidinone (5.47 g) in dry DMF (50 ml) under nitrogen and the mixture was stirred for 15 min at 5 °C. A solution of 6-bromohexyl 4-(3-iodophenyl)butyl ether (10.7 g) in DMF (30 ml) was then added dropwise over 10 min. The mixture was stirred for 2 h at ambient temperature, then poured into aqueous solution of ammonium chloride and extracted into ethyl acetate. The combined extracts were washed with water, dried (Na_2SO_4) and evaporated. The residue was purified on biotage (90 g cartridge) eluting with ether - hexane (3:2) to give *the title compound* (9.8 g). LCMS RT= 4.20 min.

viii) (5*R*)-3-(6-{4-[3-(Cyclopentylthio)phenyl]butoxy}hexyl)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

A stirred solution of (5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-{6-[4-(3-iodophenyl)butoxy]hexyl}-1,3-oxazolidin-2-one (1.8g), 1,1 bis(diphenylphosphino) ferrocene (86 mg) and tris(dibenzylideneacetone) di palladium (180mg) was stirred at room temperature in 1-methyl-2-pyrrolidinone (10ml) and triethylamine (2ml) for 10 min under nitrogen. Cyclopentyl mercaptan (0.63ml) was added and the mixture was heated at 60 °C for 1 h. The mixture was cooled, poured into water and extracted into dichloromethane. The extracts were dried (Na_2SO_4) and evaporated. The residual oil was purified on a biotage cartridge (90g) using ether-hexane (3:2) as eluent changing to ether. The appropriate fractions were evaporated to give *the title compound* (1.07g). LCMS RT = 4.31 min.

ix) (5*R*)-3-(6-{4-[3-(Cyclopentylsulfinyl)phenyl]butoxy}hexyl)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

Sodium periodate (1.5g) was added to a stirred solution of (5*R*)-3-(6-{4-[3-(cyclopentylthio)phenyl]butoxy}hexyl)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (1.0g) in ethanol (20ml) and water (10ml) at room temperature. After 2 h the solution was concentrated *in-vacuo* (ca 50% vol), diluted with water and extracted into dichloromethane. The extracts were dried (Na_2SO_4) and evaporated to dryness. The residual oil was purified on a biotage cartridge (40g) using ethyl acetate as the eluent. The appropriate fractions were evaporated to give *the title compound* (0.68g). LCMS RT = 3.66 min

x) (1*R*)-2-[(6-{4-[3-(Cyclopentylsulfinyl)phenyl]butoxy}hexyl)amino]-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol

A stirred mixture of (5*R*)-3-(6-{4-[3-(cyclopentylsulfinyl)phenyl]butoxy}hexyl)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (0.14g) and potassium trimethyl silanolate (0.45g) in tetrahydrofuran (10ml) was heated to reflux for 2 h. The mixture was poured into phoshate buffer solution (pH 5, 50ml) and extracted into ethyl acetate. The extracts were washed with water, dried (Na_2SO_4) and evaporated. The residual oil was purified on a biotage cartridge (8g) using dichloromethane-ethanol-0.88 ammonia

(100:8:1) as eluent. The appropriate fractions were evaporated to give *the title compound* (0.11g) LCMS RT = 2.89 min.

xi) 4-{(1*R*)-2-[(6-{4-[3-(Cyclopentylsulfinyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol acetate

A stirred solution of (1*R*)-2-[(6-{4-[3-(cyclopentylsulfinyl)phenyl]butoxy}hexyl)amino]-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol (0.1g) in glacial acetic acid (5ml) and water (0.2ml) was heated at 82 °C for 40 min. The solution was evaporated to dryness to give *the title compound* as a clear oil (0.075g). LCMS = 2.61 min, ES+ve 532 (MH^+).

Example 2

4-{(1*R*)-2-[(6-{4-[3-(Cyclopentylsulfinyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol acetate (Isomer 1)

i) (5*R*)-3-(6-{4-[3-(Cyclopentylsulfinyl)phenyl]butoxy}hexyl)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (Isomer 1)

Prepared using methods similar to those described in Example 1 ix)

Separation of diastereoisomers was achieved using a chiracel OD column (5 cm × 20 cm) using heptane-ethanol (4:1) as eluent. The *title compound* was obtained as a clear oil (0.198g). LCMS RT = 3.69 min.

ii) (1*R*)-2-[(6-{4-[3-(Cyclopentylsulfinyl)phenyl]butoxy}hexyl)amino]-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol (Isomer 1)

Prepared using methods similar to those described in Example 1 x)

LCMS RT = 2.90 min.

iii) 4-{(1*R*)-2-[(6-{4-[3-(Cyclopentylsulfinyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol acetate (Isomer 1)

Prepared using methods similar to those described in Example 1 xi)

LCMS RT = 2.60 min, ES+ve 532 (MH^+).

Example 3

4-{(1*R*)-2-[(6-{4-[3-(Cyclopentylsulfinyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol acetate (Isomer 2)

i) (5*R*)-3-(6-{4-[3-(Cyclopentylsulfinyl)phenyl]butoxy}hexyl)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (Isomer 2)

Prepared using methods to those described in Example 1 ix)

LCMS RT = 3.68 min.

ii) (1*R*)-2-[(6-{4-[3-(Cyclopentylsulfinyl)phenyl]butoxy}hexyl)amino]-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol (Isomer 2)

Prepared using methods similar to those described in Example 1 x)

LCMS RT = 2.89 min.

iii) 4-{(1*R*)-2-[(6-{4-[3-(Cyclopentylsulfinyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol acetate (Isomer 2)

Prepared using methods similar to those described in Example 1 xi)

LCMS RT = 2.60 min, ES+ve 532 (MH^+).

Example 4

4-{(1*R*)-2-[(6-{4-[3-(Cyclopentylsulfonyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol acetate

i) (5*R*)-3-(6-{4-[3-(Cyclopentylsulfonyl)phenyl]butoxy}hexyl)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

3--Chloroperoxy benzoic acid (0.088g) was added to a stirred, cooled (ice-bath) solution of (5*R*)-3-(6-{4-[3-(cyclopentylsulfinyl)phenyl]butoxy}hexyl)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (0.097g) in dichloromethane (10ml). The solution was stirred for 0.5 h at room temperature. The solution was diluted with dichloromethane and washed with 2N sodium hydroxide solution, water, dried (Na_2SO_4) and evaporated to give the *title compound* as a clear oil (0.085g) LCMS RT = 3.78 min.

ii) (1*R*)-2-[(6-{4-[3-(Cyclopentylsulfonyl)phenyl]butoxy}hexyl)amino]-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol

Prepared using methods to those described in Example 1 x)

LCMS RT = 2.92 min.

iii) 4-{(1*R*)-2-[(6-{4-[3-(Cyclopentylsulfonyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol acetate

Prepared using methods similar to those described in Example 1 xi)

LCMS RT = 2.66 , ES+ve 548 (MH^+).

BIOLOGICAL ACTIVITY

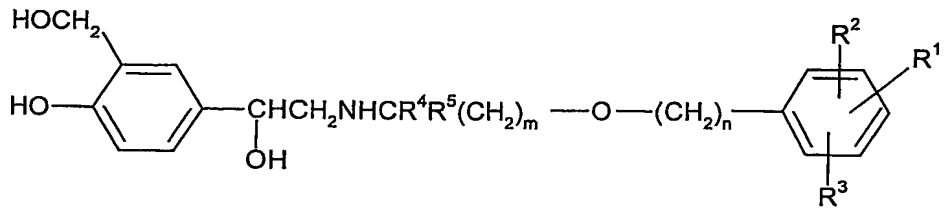
The potencies of the aforementioned compounds were determined using frog melanophores transfected with the human beta 2 adrenoreceptor. The cells were incubated with melatonin to induce pigment aggregation. Pigment dispersal was induced by compounds acting on the human beta 2 adrenoreceptor. The beta 2 agonist activity of test compounds was assessed by their ability to induce a change in light transmittance across a melanophore monolayer (a consequence of pigment dispersal). At the human beta 2 adrenoreceptor, compounds of examples 1 - 4 had IC_{50} values below 1μM.

Potency at other beta adrenoreceptor subtypes was determined using chinese hamster ovary cells transfected with either the human beta 1 adrenoreceptor or the human beta 3 adrenoreceptor. Agonist activity was assessed by measuring changes in intracellular cyclic AMP.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

Claims

1. A compound of formula (I):



(I)

or a salt, solvate, or physiologically functional derivative thereof, wherein:

m is an integer of from 2 to 8;
n is an integer of from 3 to 11,
with the proviso that m + n is 5 to 19,

R^1 is SR^6, SOR^6, or SO_2R^6,
wherein R^6 is a C_{3-7}cycloalkyl or C_{3-7}cycloalkenyl group;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, halo, phenyl, and C_{1-6}haloalkyl; and

R^4 and R^5 are independently selected from hydrogen and C_{1-4}alkyl with the proviso that the total number of carbon atoms in R^4 and R^5 is not more than 4.

2. A method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2-adrenoreceptor agonist is indicated, which comprises administration of a therapeutically effective amount of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

3. A compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy.

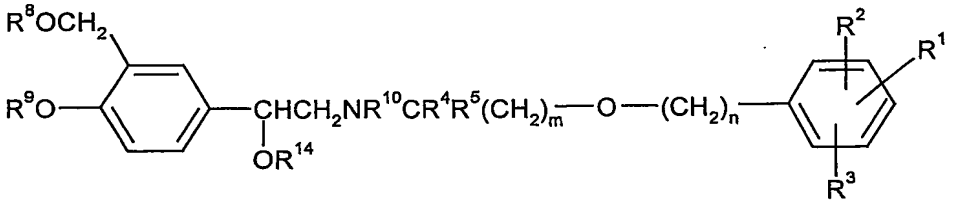
4. A pharmaceutical formulation comprising a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

5. A combination comprising a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and one or more other therapeutic ingredients.

6. The use of a compound of formula according to claim 1, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a selective β_2-adrenoreceptor agonist is indicated.

7. A process for the preparation of a compound of formula (I) according to claim 1 or a salt, solvate, or physiologically functional derivative thereof, which comprises:

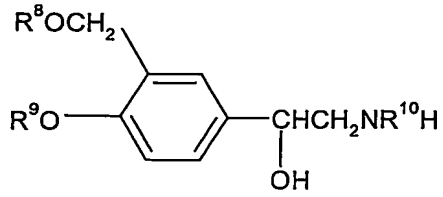
(a) deprotection of a protected intermediate, for example of formula (II):



(II)

or a salt or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, m, and n are as defined for the compound of formula (I) and R^8, R^9, and R^{10} are each independently either hydrogen or a protecting group provided that at least one of R^8, R^9, and R^{10} is a protecting group;

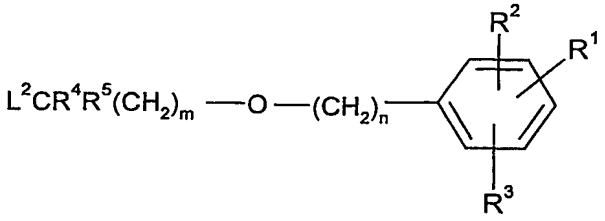
(b) alkylation of an amine of formula (X)



(X)

wherein R^8 and R^9, R^{10} and R^{14} are each independently either hydrogen or a protecting group,

with a compound of formula (XI):



(XI)

wherein R^1, R^2, R^3, R^4, R^5, m, and n are as defined for the compound of formula (I) and L^2 is a leaving group;

followed by the following steps in any order:

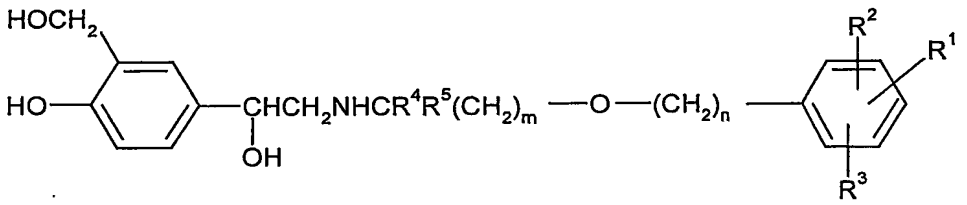
(i) optional removal of any protecting groups;

(ii) optional separation of an enantiomer from a mixture of enantiomers;

(iii) optional conversion of the product to a corresponding salt, solvate, or physiologically functional derivative thereof.

ABSTRACT

The present invention relates to novel compounds of formula (I),



(I)

to a process for their manufacture, to pharmaceutical compositions containing them, and to their use in therapy, in particular their use in the prophylaxis and treatment of respiratory diseases.

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